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Case review

# Ibogaine related sudden death: A case report

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ABSTRACT

Ibogaine is a naturally occurring alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga*. Deaths have occurred temporarily related to the use of ibogaine. However, although not licensed as therapeutic drug, and despite evidence that ibogaine may disturb the rhythm of the heart, this alkaloid is currently used as an anti-addiction drug in alternative medicine for detoxification purposes. We report the case of a man who died suddenly 12–24 h after ibogaine use for alcohol detoxification treatment. In the autopsy liver cirrhosis and heavy fatty infiltration was found. The concentration of ibogaine was 2 mg/l. The potential risks of ibogaine use, especially for persons with pathological medical background, are discussed.



## 1. Introduction

Ibogaine is a naturally occurring alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga*. The plant is mainly found in West and Central Africa and has long been used in rituals and to fight fatigue, hunger and thirst. In the last decades it drew the attention of the Western world for its potential to inhibit withdrawal symptoms associated with weaning from drugs.[1] Ibogaine has previously been reported to have central nervous system (CNS) stimulant, anxiogenic, and hallucinogenic properties.[2]

Ibogaine was administered to human subjects in a clinical Phase I dose escalation study under a physician-initiated Investigational New Drug Application approved by the FDA in 1993. The study was eventually discontinued because of disputes related to contractual and intellectual property issues; however, the available safety data indicated no adverse events.[3] Most of the available preclinical pharmacological, toxicological, and pharmacokinetic data on ibogaine are derived from research supported by NIDA between 1991 and 1995. NIDA eventually ended its ibogaine project without having initiated a clinical trial apparently because of its high cost and complexity relative to NIDA's existing resources.[4] Ibogaine's underlying structure cannot be patented because it is naturally occurring, which limits the financial incentive for its development. Ibogaine continues to be used in unregulated contexts with associated risks because of a lack of clinical and pharmaceutical standards.[5–7]

Deaths temporarily related to the use of ibogaine have been reported.[8] However, although not licensed as therapeutic drug, and despite evidence that ibogaine may disturb the rhythm of the heart, this alkaloid is currently used as an anti-addiction drug in alternative medicine for detoxification purposes (Lotsoff 2003).[9] In the present study we report the case of a man who died suddenly 12–24 h after ibogaine use for alcohol detoxification treatment.

## 2. Case report

A 52 year old man with a history of alcoholism during the last 20 years died suddenly in his house without specific symptoms. Concerning his medical history, no other problems were mentioned, except from an episode of hypokalemia and hypomagnesemia, because of which he was hospitalized. According to his wife the man had spent two days staying in a hotel with a "therapist". The "therapist" administered him several plant-derived substances so that he could face his addiction problem. He left from

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the hotel at 7.00 in the morning and he suddenly died at 23:45 in his house. His wife described him as "hypotonic" during the above time interval, but except from this no other symptom was mentioned.

The "therapist" was asked by the police to bring the drugs he was using for the detoxification treatment. He claimed that plant extracts from Uncaria tomentosa, Skutellaria lateriflora, Medicago sativa. Quassia amara and Silene capensis were also admimistered per os as capsules to the patient, but, as the therapist supported, no samples have been left.

On the next day, the dead man was referred to the Department of Forensic Medicine and Toxicology for autopsy. The external examination of the body did not reveal any significant finding. During the macroscopical examination of the organs, the following findings were shown: a) cerebrospinal fluid shunt, b) slightly increased weight of the heart (480 g) with coronary lesions type Vb causing a 40–45% occlusion of the left and right coronary artery, b) pulmonary edema and c) a small yellowish, nodular and firm liver indicating cirrhosis and heavy fatty infiltration. The histopathological examination confirmed the above mentioned macroscopical findings. Moreover, it showed recent ischemia of myocardium, an almost total fatty infiltration of the liver (more than 90%) and hemosiderin containing macrophages in the lungs.

Blood, urine and stomach content were collected for toxicolocical analysis. Blood samples were obtained from the femoral artery by percutaneous puncture and they were placed in tubes containing a fluoride preservative to reach a final concentration of 1–5% by weight. Urine was obtained by direct puncture with needle and syringe of the exposed bladder once the abdomen was opened. Finally, stomach content was obtained during dissection of the stomach after clamping the lower end of the esophagus and the pylorus.[10] The toxicological examination revealed the presence of ibogaine at a concentration of 2 mg/L of blood. Postmortem redistribution of ibogaine does not seem to constitute a problem, given that no substantial differences have been shown between concentrations from the femoral and cardiac or vena cava sites.[8] Ibogaine and its metabolite noribogaine were also detected in the urine. Ibogaine was probably administered with Silene capensis (one of the above mentioned plant extracts, of which no sample was delivered), given that there are products provided via Internet in which the above substances are combined.[11]

The death was considered as cardiac, ibogaine-related death, on the ground of coronary disease and serious liver disease.

## 3. Discussion

Ibogaine is a schedule I substance in the United States, and similarly is illegal in France, Denmark, Sweden, Belgium, Switzerland, and Australia.[4,8] In most of the countries, it is illegal or not officially approved. In Greece, it is not Government licensed, but there are Internet sites in which ibogaine treatments offered in Athens are advertised.[12] Lay providers administer ibogaine in non medical settings and have accounted for the majority of treatments.[4]

Unexplained death or adverse events following the use of ibogaine have been described before incidentally; they have rarely been related with ibogaine blood levels. In their recent study, Alper et al. reviewed all available autopsy, toxicological and investigative reports for the consecutive cases of all known fatalities temporarily related to the use of ibogaine from 1990 through 2008.[8] Nineteen individuals (15 men, four women between 24 and 54 years old) were known to have died within 1.5–76 h after taking ibogaine. The clinical and postmortem evidence did not suggest a characteristic syndrome of neurotoxicity. The lack of clinical and pharmaceutical controls in settings in which ibogaine has been given, and the limited data regarding toxic concentrations of ibogaine in humans make the determination of the causes of these deaths difficult. Nonetheless, advanced comorbidities and contributing conditions appear to include preexisting medical, particularly cardiovascular, disease and drug use around the time of treatment.

Although preclinical toxicological testing by NIDA did not indicate prolongation of the QT interval, it has been observed during ibogaine treatments with continuous ECG monitoring,[13] which is associated with "torsade de pointes (TdP)", a morphologically distinctive polymorphic ventricular tachycardia. In their recent study, Paling et al. describe two cases of a 49 and 33-year old male, respectively, who presented a strikingly prolonged QT and ventricular tachycardia or "torsade de pointes", after ibogaine use as anti-addictive treatment[6] Neither others drugs have been taken, nor a pathological background existed. The patients were admitted to Intensive Unit Care and were discharged some days later. A similar case of ventricular tachyardia has been described by Pleskovic et al.[7]

The mechanism through which ibogaine may exert its arrythmiogenic effects is unclear. It has been demonstrated to have low micromolar affinity for sodium channels,[14] which could possibly relate to cardiac risk in view of the possible association of sodium channel blockade with slowing of intraventricular conduction and the subsequent development of a re-entrant circuit resulting in ventricular tachyarrhythmia,[15,16] The reduction of human ether-a-go-go-related gene potassium channels may be another possible mechanism by which ibogaine may generate life-threatening cardiac arrhythmias (Koenig 2012).[17]

However, several other situations and comorbities may induce prolongation of QT, complicating the decision about the causality of ibogaine use with the adverse situation. In our case, the man had hepatic cirrhosis and fatty infiltration. Fatty infiltration of the liver has been linked with prolongation of QT, especially in alcoholics. On the other side the action of ibogaine may be prolongated in the presence of hepatic disease, as ibogaine during its biotransformation undergoes desmethylation by the action of cytochrome P450 enzymes to its principal metabolite, noribogaine or 12-hydroxyibogamine.[18]

Another situation which must be taken under account is the fact that a 40–45% occlusion of coronary arteries was observed (moderate atherosclerosis), as well as a slightly increased weight of heart. Although not rare in a man older than 50 year old, the above findings are abnormal and may cause arrhythmias or ischemia of myocardium.[19,20]

The frequently altered nutritional status of substance and more specifically alcohol abusers puts them at risk of hypomagnesemia and hypokalemia,[21] which are associated with QT prolongation, as it has shown for other causes of altered nutritional status, such as bulimia and anorexia.[22] The patient's wife described an episode of hypomagnesemia and hypokalemia in the past, because of which he needed hospitalization.

Alcohol use is associated with prolongation of the QT interval both acutely[23,24] and during withdrawal.[25,26] Sudden death due to prolongation of QT to alcoholics with alcoholic liver disease, has been also suggested.[27] Epileptic seizures, even in the absence of substance use or withdrawal, are an independent risk factor for QT prolongation.[28]

The main problem in attributing the death only to ibogaine use is the lack of evidence concerning the toxic concentrations of ibogaine in blood. The available data do not provide a basis for a reliable estimate of them. In cases of deaths in which ibogaine was detected, the blood ibogaine concentration ranged from 0.24 to 9.3 mg/L.[8] In the present case, the relative concentration of ibogaine was 2 mg/L. The cause of death may represent a complex

interaction involving a substance against a backdrop of systemic medical illness related to addiction (hepatic cirrhosis and fatty infiltration, in our case). Although controlled clinical trials proving the safety, or not, of the substance have never been carried out, there are strong indications that ibogaine may represent a risk factor when combined with other substances or on the ground of serious systemic diseases, mainly cardiovascular and liver diseases. For the above reasons, even in countries where its use is permitted, pretreatment screening including basic blood chemistries and electrocardiograph, the exclusion of patients with significant medical, particularly cardiac illness, and the recognition of the need to stabilize physical dependence on alcohol and benzodiazepines prior to ibogaine treatment has gradually become more widely accepted norms in the settings of ibogaine use.[9]

In conclusion, ibogaine use as an anti-addiction therapy has been a controversial matter for many years. Its usefulness has been discussed, as much as the potential risks it poses, especially for people with pathological background or co-use of other drugs. To date, there is no published data from a controlled clinical trial, but only anecdotal reports concerning the efficacy of ibogaine in the treatment of drug addictions or adverse events after ibogaine use. The Internet has increasingly become a portal for the trade of and access to several substances, including ibogaine. When products are offered via internet, the concern for lack of objective information arises, including potential risks to health. The present case represents such a case in which the provision of an unshceduled in Greece substance was performed via Internet, and the health risks were underestimated. Until a more detailed and complementary approach be performed about the matter, it must be widely understood that ibogaine should not in any case be considered as an "innocent" plant extract, with no health risks, that could be used with no caution or medical supervision.

*Ethical approval*

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

*Conflict of interest*

There are no financial or other relationships that might lead to a conflict of interest or a statement that the authors do not have any conflict of interest.

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